

# Global dynamics of a HTLV-I infection model with CTL response \*

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## Abstract

In this paper, a HTLV-I infection model with CTL response is considered. To account for a series of events in infection process, we incorporate a intracellular time delay in the model. We prove that the global dynamics are determined by two threshold parameters  $R_0$  and  $R_1$ , basic reproduction numbers for viral infection and for CTL response, respectively. If  $R_0 < 1$ , the infection-free equilibrium  $P_0$  is globally asymptotically stable. If  $R_1 < 1 < R_0$ , the asymptomatic-carrier equilibrium  $P_1$  is globally asymptotically stable. If  $R_1 > 1$ , there exists a unique HAM/TSP equilibrium  $P_2$ , and the equilibrium  $P_2$  is asymptotically stable under certain conditions.

**2010 AMS Subject Classification:** 34K20, 92D25

**Keywords:** HTLV-I infection; CTL response; time delay; Lyapunov functionals; global stability

## 1 Introduction

HTLV-I is an abbreviation for the human T-cell lymphotropic virus type 1, also called the Adult T-cell lymphoma virus type 1, a virus that has been seriously implicated in several kinds of diseases. The Human T-lymphotropic virus Type I (HTLV-I)

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\*This research is supported by National Natural Science Foundation of China (No.11031002) and Research Fund for the Doctoral Program of Higher Education of China (No.20122302110044).

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is a human RNA retrovirus that is known to cause a type of cancer, referred to as adult T-cell leukemia and lymphoma, and a demyelinating disease called HTLV-I associated myelopathy/Tropical spastic paraparesis (HAM/TSP). HTLV-I is one of a group of closely related primate T lymphotropic viruses (PTLVs). Approximately 20 to 40 million people are infected by HTLV-I worldwide. The majority of HTLV-I infected individuals remain lifelong asymptomatic carriers. Approximately 0.25%-3.8% of individuals develop HAM/TSP, and another 2%-3% develop ATL [1]. HTLV-I infection is achieved through cell-to-cell contact [2]. The immune system reacts to HTLV-I infection with a strong cytotoxic T-lymphocyte (CTL) response. HTLV-I infection models have been studied by many researchers [1,4,5] and mathematical models have been developed to describe the interaction in vivo HTLV-I, the CD4<sup>+</sup> target cells, and the CTL immune response.

In order to establish the model, we partition the CD4<sup>+</sup> T-cell population into uninfected and infected compartments, whose numbers at time  $t$  are denoted by  $x(t), y(t)$ , respectively. Let  $z(t)$  denote the number of HTLV-I-specific CD8<sup>+</sup> CTLs at time  $t$ . The production of health CD4<sup>+</sup> T cells is assumed to at a constant rate  $\lambda$ . Since HTLV-I infection occurs by cell-to-cell contact between infected cells and uninfected cells, a bilinear incidence  $\beta xy$  is assumed. CTL-driven elimination of infected CD4<sup>+</sup> cells is assumed to be of the form  $\gamma yz$ , where  $\gamma$  is the rate of CTL elimination. The CTL response to the HTLV-I infection is modeled by a general function  $f(y, z)$ , dependent of the number of CTLs and infected CD4<sup>+</sup> T cells. The turnover rates of uninfected and infected CD4<sup>+</sup> are  $d_1$  and  $d_2$ , respectively, and the turnover rate of CTLs is  $d_3$ . All parameters are assumed to be positive. Based on the preceding assumptions, we can obtain the following basic HTLV-I infection model with CTL response

$$(1.1) \quad \begin{cases} x'(t) = \lambda - d_1x(t) - \beta x(t)y(t), \\ y'(t) = \beta x(t)y(t) - d_2y(t) - \gamma y(t)z(t), \\ z'(t) = f(y, z) - d_3z(t). \end{cases}$$

This model with several forms of CTL response function  $f(y, z)$  have been considered and analyzed by Nowak [13] and Wodarz, Nowak and Bangham [14], respectively.

However, there exist obvious delays in the infection process. We briefly summarize the main stages following Li and Shu [6]. The first stage of infection is the period between the viral entry of a target cell and integration of viral DNA into the host genome. The second stage is the period from the integration of viral DNA to the transcriptase of viral RNA and translation of viral proteins. The third stage is the period between the transcription of viral RNA and the release and maturation of virus. To account for these events in the infection process, we incorporate a time delay in the model. Therefore, in the present paper, we consider the model in the

following form:

$$(1.2) \quad \begin{cases} x'(t) = \lambda - d_1 x(t) - \beta x(t)y(t), \\ y'(t) = \beta x(t - \tau)y(t - \tau) - d_2 y(t) - \gamma y(t)z(t), \\ z'(t) = f(y, z) - d_3 z(t). \end{cases}$$

Here we use  $f(y, z) = \mu y(t)z(t)$ .

The organization of this paper is as follows. In the next section, we discuss the feasible region for system (1.2) and derive two threshold parameters  $R_0$  and  $R_1$ , and show existence of equilibria in relation to values of  $R_0$  and  $R_1$ . In Section 3 and 4, global stability of  $P_0$  when  $R_0 < 1$  and global stability of  $P_1$  when  $R_1 < 1 < R_0$  are discussed. The stability of equilibrium  $P_2$  is investigated in Section 5. Numerical simulations are presented in Section 6, to illustrate and support our analyzed results. The paper ends with brief remarks.

## 2 Preliminaries

To investigate the dynamics of system (1.2), we need to consider a suitable phase space and a feasible region. For  $\tau > 0$ , we denote by  $\mathcal{C} = \mathcal{C}([-\tau, 0], \mathbb{R})$  the Banach space of continuous real-valued function on the interval  $[-\tau, 0]$ , with norm  $\|\phi\| = \sup_{-\tau \leq \theta \leq 0} |\phi(\theta)|$  for  $\phi \in \mathcal{C}$ . The nonnegative cone of  $\mathcal{C}$  is defined as  $\mathcal{C}^+ = \mathcal{C}([-\tau, 0], \mathbb{R}_+)$ . Initial conditions for system (1.2) are chosen as

$$(2.1) \quad \varphi \in \mathcal{C}^+ \times \mathcal{C}^+ \times \mathbb{R}_+, \varphi = (\varphi_1, \varphi_2, \varphi_3) \text{ with } \varphi_i(0) > 0, i = 1, 2 \text{ and } \varphi_3 > 0.$$

**Proposition 2.1.** *Under initial condition (2.1), all solutions of system (1.2) are positive and ultimately bounded in  $\mathcal{C} \times \mathcal{C} \times \mathbb{R}$ . Furthermore, all solutions eventually enter and remain in the following bounded and positively invariant region:*

$$\Gamma = \{(x, y, z) \in \mathcal{C}^+ \times \mathcal{C}^+ \times \mathbb{R}_+ : \|x\| \leq \frac{\lambda}{d_1} + \varepsilon, \|x + y\| \leq \frac{\lambda}{d} + \varepsilon, \|x + y + \frac{\gamma}{\mu} z\| \leq \frac{\lambda}{d} + \varepsilon\},$$

where  $d = \min\{d_1, d_2, d_3\} > 0, \tilde{d} = \min\{d_1, d_2\} > 0, \varepsilon$  is arbitrarily small positive number.

*Proof.* First, we prove that  $x(t)$  is positive for  $t \geq 0$ . Assuming the contrary and letting  $t_1 > 0$  be the first time such that  $x(t_1) = 0$ , by the first equation of system (1.2), we have  $x'(t_1) = \lambda > 0$ , and hence  $x(t) < 0$  for  $t \in (t_1 - \eta, t_1)$  and sufficiently small  $\eta$ . This contradicts  $x(t) > 0$  for  $t \in [0, t_1)$ . It follows that  $x(t) > 0$  for  $t > 0$  as long as  $x(t)$  exists. Similarly, we can show that  $y(t) > 0$  for  $t > 0$ . From the third equation of (1.2), we have

$$z(t) = z(0)e^{\int_0^t (\mu y(\theta) - d_3) d\theta}.$$

It follows that  $z(t) > 0$  for  $t > 0$ .

Next we show that positive solutions of (1.2) are ultimately bounded for  $t \geq 0$ . From the first equation of system (1.2), we obtain

$$x'(t) \leq \lambda - d_1 x(t), \quad t \geq 0,$$

and thus

$$\limsup_{t \rightarrow \infty} x(t) \leq \frac{\lambda}{d_1}.$$

Adding the first two equations of (1.2), we get

$$(x(t) + y(t + \tau))' \leq \lambda - \tilde{d}(x(t) + y(t + \tau)), \quad t \geq 0,$$

where  $\tilde{d} = \min\{d_1, d_2\}$ . Thus

$$\limsup_{t \rightarrow \infty} (x(t) + y(t + \tau)) \leq \frac{\lambda}{\tilde{d}}.$$

Adding all the equations of (1.2), we get

$$\begin{aligned} (x(t) + y(t + \tau) + \frac{\gamma}{\mu} z(t + \tau))' &= \lambda - d_1 x(t) - d_2 y(t + \tau) - \frac{\gamma}{\mu} d_3 z(t + \tau) \\ &\leq \lambda - d(x(t) + y(t + \tau) + \frac{\gamma}{\mu} z(t + \tau)), \end{aligned}$$

where  $d = \min\{d_1, d_2, d_3\}$ . Thus

$$\limsup_{t \rightarrow \infty} (x(t) + y(t + \tau) + \frac{\gamma}{\mu} z(t + \tau)) \leq \frac{\lambda}{d}.$$

Based on the discussion above, we have obtained that all solutions of system (1.2) with initial condition (2.1) eventually enter and remain in the region  $\Gamma$ . Therefore, the solutions of system (1.2) with initial condition (2.1) are ultimately uniformly bounded in  $\mathcal{C} \times \mathcal{C} \times \mathbb{R}$  by  $(\lambda/d) + \varepsilon$ . It is not difficult to verify that the region  $\Gamma$  is positive invariant for system (1.2).  $\square$

As a consequence of proposition 2.1, we know that the dynamics of system (1.2) can be analyzed in the following bounded feasible region

$$\Gamma = \{(x, y, z) \in \mathcal{C}^+ \times \mathcal{C}^+ \times \mathbb{R}_+ : \|x\| \leq \frac{\lambda}{d_1} + \varepsilon, \|x + y\| \leq \frac{\lambda}{\tilde{d}} + \varepsilon, \|x + y + \frac{\gamma}{\mu} z\| \leq \frac{\lambda}{d} + \varepsilon\}.$$

Furthermore, the region  $\Gamma$  is positively invariant with respect to system (1.2) and the model is well posed.

System (1.2) always has an infection-free equilibrium  $P_0 = (x_0, 0, 0)$ ,  $x_0 = \frac{\lambda}{d_1}$ . In addition to  $P_0$ , the system can have two chronic-infection equilibria  $P_1 = (\bar{x}, \bar{y}, 0)$  and  $P_2 = (x^*, y^*, z^*)$  in  $\Gamma$ , where  $\bar{x}, \bar{y}, x^*, y^*$  and  $z^*$  are all positive. At equilibrium

$P_1$ , the HTLV-I infection is persistent with a constant proviral load  $\bar{y} > 0$ , whereas CTL response is absent, so is the risk for developing HAM/TSP. This corresponds to the situation of an asymptotic carrier. At equilibrium  $P_2$ , both the proviral load and CTL response persist at a constant level. This corresponds to the situation of a HAM/TSP patient. Which of the three steady-states is the final outcome of the system will be determined by a combination of two threshold parameters.

$$(2.2) \quad R_0 = \frac{\lambda\beta}{d_1d_2}, \quad R_1 = \frac{\lambda\beta\mu}{d_1d_2\mu + \beta d_2d_3}.$$

They are called the basic reproduction numbers for viral infection and for CTL response, respectively (Gomez-Acevedo et al. [4]). We note that  $R_1 < R_0$  always holds.

It can be verified that the carrier equilibrium  $P_1 = (\bar{x}, \bar{y}, 0)$  exists if and only if  $R_0 > 1$  and that

$$(2.3) \quad \bar{x} = \frac{d_2}{\beta} = \frac{\lambda}{d_1R_0}, \quad \bar{y} = \frac{\lambda\beta - d_1d_2}{\beta d_2} = \frac{d_1(R_0 - 1)}{\beta}$$

The coordinates of the HAM/TSP equilibrium  $P_2 = (x^*, y^*, z^*)$  are given by

$$(2.4) \quad x^* = \frac{\lambda\mu}{d_1\mu + \beta d_3} = \frac{d_2R_1}{\beta}, y^* = \frac{d_3}{\mu}, z^* = \frac{\beta\lambda\mu - d_1d_2\mu - \beta d_2d_3}{(d_1\mu + \beta d_3)\gamma} = \frac{d_1d_2\mu + \beta d_2d_3}{(d_1\mu + \beta d_3)\gamma}(R_1 - 1).$$

Therefore,  $P_2$  exists in the interior of  $\Gamma$  if and only if  $R_1 > 1$ . We thus have the following result.

**Proposition 2.2.** *If  $R_0 < 1$ ,  $P_0 = (\frac{\lambda}{d_1}, 0, 0)$  is the only equilibrium in  $\Gamma$ . If  $R_1 < 1 < R_0$ , the carrier equilibrium  $P_1 = (\bar{x}, \bar{y}, 0)$  exists and is the only chronic-infection equilibrium in  $\Gamma$ . If  $R_1 > 1$ , both the carrier equilibrium  $P_1$  and the HAM/TSP equilibrium  $P_2 = (x^*, y^*, z^*)$  exist.*

### 3 Global stability of $P_0$ when $R_0 < 1$

In this section, we rigorously show that when  $R_0 < 1$ , the infection-free equilibrium  $P_0$  is globally asymptotically stable in  $\Gamma$ .

**Theorem 3.1.** *If  $R_0 < 1$ , then the infection-free equilibrium  $P_0$  of system (1.2) is globally asymptotically stable in  $\Gamma$ . If  $R_0 > 1$ , then  $P_0$  is unstable.*

*Proof.* Firstly we prove  $P_0$  is globally attractive in  $\Gamma$  if  $R_0 < 1$ . To prove this, we consider a Lyapunov functional  $L : \mathcal{C} \times \mathcal{C} \times \mathbb{R} \rightarrow \mathbb{R}$  given by

$$(3.1) \quad L(x_t, y_t, z(t)) = x_0 g\left(\frac{x_t(0)}{x_0}\right) + y_t(0) + \beta \int_{-\tau}^0 x_t(\theta) y_t(\theta) d\theta,$$

where  $x_0$  is the first coordinate of  $P_0$ ,  $g(u) = u - \ln u - 1, u > 0$ . Here  $x_t(s) = x(t+s), y_t(s) = y(t+s)$  for  $s \in [-\tau, 0]$ , and thus  $x(t) = x_t(0), y(t) = y_t(0)$  in this notation. Calculating the time derivative of  $L$  along the solution in  $\Gamma$  of system (1.2), we obtain

$$\begin{aligned} L'|_{(1.2)} &= \lambda - d_1 x(t) - \frac{x_0 \lambda}{x(t)} + d_1 x_0 + x_0 \beta y(t) - d_2 y(t) - \gamma y(t) z(t) \quad \left( x_0 = \frac{\lambda}{d_1} \right) \\ &= d_1 x_0 \left( 2 - \frac{x(t)}{x_0} - \frac{x_0}{x(t)} \right) + d_2 y(t) (R_0 - 1) - \gamma y(t) z(t). \end{aligned}$$

Therefore,  $R_0 < 1$  ensures that  $L'|_{(1.2)} \leq 0$  is satisfied in  $\Gamma$ . Clearly, for  $(x_t, y_t, z(t)) \in \Gamma$  satisfying  $L' = 0$  if and only if  $x(t) = x_0, y(t) = 0$  and  $z(t) \in \mathbb{R}_+$ . Clearly,  $(x_0, 0, z(t))$  is a solution of (1.2) if and only if  $z(t) \equiv 0$ . This implies that the maximal invariant set of system (1.2) in  $\{L'|_{(2.1)} = 0\}$  is the set  $M = \{(x_0, 0, 0)\}$ . By the LaSalle-Lyapunov theorem (LaSalle and Lefschetz [15] theorem 3.4.7), we conclude that  $M$  is globally attractive in  $\Gamma$  if  $R_0 < 1$ . So  $P_0$  is globally attractive in  $\Gamma$ .

Secondly we prove that  $P_0$  is locally asymptotically stable. The characteristic equation associated with the linearization of system (1.2) at  $P_0$  is given by

$$(3.2) \quad (\xi + d_1)(\xi + d_3) \left( \xi + d_2 - \frac{\beta \lambda}{d_1} e^{-\xi \tau} \right) = 0.$$

Obviously we have  $\xi_1 = -d_1 < 0, \xi_2 = -d_3 < 0$ , and we can easily prove that all roots of the equation  $\xi + d_2 - \frac{\beta \lambda}{d_1} e^{-\xi \tau} = 0$  have negative real parts when  $R_0 < 1$  with  $\tau \geq 0$ . So when  $R_0 < 1$ ,  $P_0$  is locally asymptotically stable.

From global attraction and locally asymptotical stability of  $P_0$ , we obtain that  $P_0$  is globally asymptotically stable in  $\Gamma$  when  $R_0 < 1$ .

Next, we show that  $P_0$  is unstable when  $R_0 > 1$ . The characteristic equation associated with the linearization of system (1.2) at  $P_0$  is

$$(\xi + d_1)(\xi + d_3) \left( \xi + d_2 - \frac{\beta \lambda}{d_1} e^{-\xi \tau} \right) = 0.$$

Now we consider equation  $\xi + d_2 - \frac{\beta \lambda}{d_1} e^{-\xi \tau} = 0, \tau \geq 0$ . The curve  $w = \xi + d_2$  and the curve  $w = \frac{\beta \lambda}{d_1} e^{-\xi \tau}$  must have intersection point in the first quadrant when  $R_0 > 1$ . So the equation

$$(\xi + d_1)(\xi + d_3) \left( \xi + d_2 - \frac{\beta \lambda}{d_1} e^{-\xi \tau} \right) = 0$$

has at least one positive root. Hence  $P_0$  is unstable when  $R_0 > 1$ . □

## 4 Global stability of $P_1$ when $R_1 < 1 < R_0$

In this section, we shall study the global stability of the fixed point  $P_1$  when  $R_1 < 1 < R_0$ . The main result is the followings.

**Theorem 4.1.** *If  $R_1 < 1 < R_0$ , then the equilibrium  $P_1$  is globally asymptotically stable in  $\Gamma \setminus \{x - \text{axis}\}$ . If  $R_1 > 1$ , then  $P_1$  is unstable.*

*Proof.* Let  $g(u) = u - \ln u - 1, u > 0$ .  $P_1 = (\bar{x}, \bar{y}, 0)$  is the carrier equilibrium.

Define a Lyapunov functional  $V : \mathcal{C} \times \mathcal{C} \times \mathbb{R} \rightarrow \mathbb{R}$

$$(4.1) \quad V(x_t, y_t, z(t)) = \bar{x}g\left(\frac{x_t(0)}{\bar{x}}\right) + \bar{y}g\left(\frac{y_t(0)}{\bar{y}}\right) + \frac{\gamma}{\mu}z(t) + \beta\bar{x}\bar{y} \int_{-\tau}^0 g\left(\frac{x_t(\theta)y_t(\theta)}{\bar{x}\bar{y}}\right) d\theta.$$

Calculating the time derivative of  $V$  along solution of system (1.2), we obtain

$$\begin{aligned} V'|_{(1.2)} = & \lambda - d_1x(t) - \beta x(t)y(t) - \bar{x} \left( \frac{\lambda}{x(t)} - d_1 - \beta y(t) \right) + \beta x(t-\tau)y(t-\tau) - d_2y(t) \\ & - \gamma y(t)z(t) - \bar{y} \left( \frac{\beta x(t-\tau)y(t-\tau)}{y(t)} - d_2 - \gamma z(t) \right) + \gamma y(t)z(t) - \frac{\gamma}{\mu}d_3z(t) \\ & + \beta\bar{x}\bar{y} \left( \frac{x(t)y(t) - x(t-\tau)y(t-\tau)}{\bar{x}\bar{y}} - \ln \frac{x(t)y(t)}{\bar{x}\bar{y}} + \ln \frac{x(t-\tau)y(t-\tau)}{\bar{x}\bar{y}} \right). \end{aligned}$$

Using  $\lambda = d_1\bar{x} + \beta\bar{x}\bar{y}$  and  $d_2 = \beta\bar{x}$ , it follows that

$$\begin{aligned} V'|_{(1.2)} = & d_1\bar{x} \left( 2 - \frac{x(t)}{\bar{x}} - \frac{\bar{x}}{x(t)} \right) - \beta\bar{x}\bar{y} \left( \frac{\bar{x}}{x(t)} - 1 - \ln \frac{\bar{x}}{x(t)} \right) - \beta\bar{x}\bar{y} \ln \frac{\bar{x}}{x(t)} \\ & - \beta\bar{x}\bar{y} \left( \frac{x(t-\tau)y(t-\tau)}{\bar{x}\bar{y}(t)} - 1 - \ln \frac{x(t-\tau)y(t-\tau)}{\bar{x}\bar{y}(t)} \right) \\ & - \beta\bar{x}\bar{y} \ln \frac{x(t-\tau)y(t-\tau)}{\bar{x}\bar{y}(t)} + \gamma\bar{y}z(t) - \frac{\gamma}{\mu}d_3z(t) \\ & - \beta\bar{x}\bar{y} \ln \frac{x(t)y(t)}{\bar{x}\bar{y}} + \beta\bar{x}\bar{y} \ln \frac{x(t-\tau)y(t-\tau)}{\bar{x}\bar{y}} \\ = & d_1\bar{x} \left( 2 - \frac{x(t)}{\bar{x}} - \frac{\bar{x}}{x(t)} \right) - \beta\bar{x}\bar{y}g\left(\frac{\bar{x}}{x(t)}\right) - \beta\bar{x}\bar{y}g\left(\frac{x(t-\tau)y(t-\tau)}{\bar{x}\bar{y}(t)}\right) \\ & + \gamma \left( \bar{y} - \frac{d_3}{\mu} \right) z(t) \\ = & d_1\bar{x} \left( 2 - \frac{x(t)}{\bar{x}} - \frac{\bar{x}}{x(t)} \right) - \beta\bar{x}\bar{y} \left[ g\left(\frac{\bar{x}}{x(t)}\right) + g\left(\frac{x(t-\tau)y(t-\tau)}{\bar{x}\bar{y}(t)}\right) \right] \\ & + \frac{\gamma(d_1\mu + \beta d_3)}{\beta\mu}(R_1 - 1)z(t) \leq 0, \end{aligned}$$

when  $R_1 < 1$ . Furthermore,  $V' = 0 \Leftrightarrow x(t) = \bar{x}, y(t) = \bar{y}, z(t) = 0$ , and thus the maximal invariant set in the set  $\{V' = 0\}$  is the singleton  $\{P_1\}$ . Therefore,  $P_1$  is globally attractive in  $\Gamma \setminus \{\text{x-axis}\}$  when  $R_1 < 1$ . Along the invariant x-axis, solutions converge to the infection-free equilibrium  $P_0$ .

We investigate local stability of  $P_1$  in following. The characteristic equation associated with the linearization of system (1.2) at  $P_1$  is

$$(4.2) \quad (\xi + d_3 - \mu\bar{y})(\xi^2 + (d_1 + d_2 + \beta\bar{y})\xi + d_1d_2 + d_2\beta\bar{y} - (\xi + d_1)\beta\bar{x}e^{-\xi\tau}) = 0.$$

We easily get  $\xi_1 = \mu\bar{y} - d_3 < 0$  when  $R_1 < 1$ . Next we consider the following equation

$$(4.3) \quad \xi^2 + (d_1 + d_2 + \beta\bar{y})\xi + d_1d_2 + d_2\beta\bar{y} - (\xi + d_1)\beta\bar{x}e^{-\xi\tau} = 0.$$

Using  $\bar{y} = \frac{\lambda\beta - d_1d_2}{\beta d_2}$ ,  $\bar{x} = \frac{d_2}{\beta}$ , we obtain

$$(4.4) \quad \xi^2 + \frac{d_2^2 + \lambda\beta}{d_2}\xi + \lambda\beta - d_2(\xi + d_1)e^{-\xi\tau} = 0.$$

The Eq. (4.4) with  $\tau = 0$  is  $\xi^2 + \frac{\lambda\beta}{d_2}\xi + \lambda\beta - d_1d_2 = 0$ , whose roots have negative real parts if  $R_1 < 1 < R_0$ . Now we consider the roots of the equation (4.4) with  $\tau > 0$ . Denotes  $a_1 = \frac{d_2^2 + \lambda\beta}{d_2}$ ,  $a_2 = \lambda\beta$ ,  $b_1 = d_2$  and  $b_2 = d_1d_2$ . Then Eq. (4.4) becomes

$$(4.5) \quad \xi^2 + a_1\xi + a_2 - (b_1\xi + b_2)e^{-\xi\tau} = 0.$$

Assuming  $\xi = i\omega$  ( $\omega > 0$ ) is a purely imaginary root of the equation (4.5) for  $\tau > 0$ . Substituting  $\xi = i\omega$  into the equation and separating the real and imaginary parts, we obtain

$$(4.6) \quad \begin{aligned} a_2^2 - \omega^2 &= b_1\omega \sin \omega\tau + b_2 \cos \omega\tau, \\ a_1\omega &= b_1\omega \cos \omega\tau - b_2 \sin \omega\tau. \end{aligned}$$

Squaring and adding both equations of (4.6) leads to

$$F(\omega) = \omega^4 + (a_1^2 - 2a_2 - b_1^2)\omega^2 + a_2^2 - b_2^2 = 0.$$

Let

$$G(u) = u^2 + (a_1^2 - 2a_2 - b_1^2)u + a_2^2 - b_2^2 = 0.$$

We easily find that  $a_1^2 - 2a_2 - b_1^2 = \frac{\lambda^2\beta^2}{d_2} > 0$ , and  $a_2^2 - b_2^2 = \lambda^2\beta^2 - d_1^2d_2^2 > 0$  for  $R_1 < 1 < R_0$ . Therefore, the equation  $G(u) = 0$  has no positive roots. Namely, the equation  $F(\omega) = 0$  has no positive roots. Thus the equation (4.5) has no purely imaginary roots. Notice that 0 is not the root of the equation (4.5). We obtain that all roots of the characteristic equation (4.2) have negative real parts. So  $P_1$  is locally asymptotically stable for  $R_1 < 1 < R_0$ .



From global attraction and locally asymptotical stability of  $P_1$ , the equilibrium  $P_1$  is globally asymptotically stable in  $\Gamma \setminus \{x - axis\}$ .

For  $R_1 > 1$ , the characteristic equation has a positive root given by

$$\xi_1 = \mu\bar{y} - d_3 > 0.$$

Thus  $P_1$  is unstable when  $R_1 > 1$ .

□

## 5 Dynamics when $R_1 > 1$

We have shown in above sections that, if  $R_1 > 1$  both the equilibrium  $P_0$  and the carrier equilibrium  $P_1$  are unstable. And the HAM/TSP equilibrium  $P_2$  exists in the interior of  $\Gamma$ . We will investigate the stability of  $P_2$  in this section.

The characteristic equation associated with the linearization of system (1.2) at  $P_2$  is

$$(5.1) \quad \begin{aligned} &\xi^3 + (d_1 + d_2 + \beta y^* + \gamma z^*)\xi^2 + (d_1 d_2 + \mu \gamma y^* z^* + \gamma d_1 z^* + \beta d_2 y^* + \beta \gamma y^* z^*)\xi \\ &+ d_1 d_3 \gamma z^* + \beta \gamma d_3 y^* z^* + e^{-\xi\tau}(-\beta x^* \xi^2 - \beta d_1 x^* \xi) = 0. \end{aligned}$$

Using  $\gamma z^* = \beta x^* - d_2$  and the expression of  $x^*, y^*, z^*$ , we get

$$(5.2) \quad \begin{aligned} &\xi^3 + (d_1 + \beta x^* + \beta y^*)\xi^2 + (\beta d_1 x^* + \beta^2 x^* y^* + \beta d_3 x^* - d_2 d_3)\xi \\ &+ d_1 d_3 \beta x^* - d_1 d_2 d_3 + \beta^2 d_3 x^* y^* - \beta d_2 d_3 y^* + e^{-\xi\tau}(-\beta x^* \xi^2 - \beta d_1 x^* \xi) = 0. \end{aligned}$$

Let

$$\begin{aligned} a_2 &= d_1 + \beta x^* + \beta y^* (> 0), a_1 = \beta d_1 x^* + \beta^2 x^* y^* + \beta d_3 x^* - d_2 d_3, \\ a_0 &= d_1 d_3 \beta x^* - d_1 d_2 d_3 + \beta^2 d_3 x^* y^* - \beta d_2 d_3 y^* (> 0), \\ b_2 &= -\beta x^* (< 0), b_1 = -\beta d_1 x^* (< 0). \end{aligned}$$

Then the equation (5.2) changes into

$$(5.3) \quad \xi^3 + a_2 \xi^2 + a_1 \xi + a_0 + e^{-\xi\tau}(b_2 \xi^2 + b_1 \xi) = 0.$$

When  $\tau = 0$ , the equation (5.3) becomes

$$(5.4) \quad \xi^3 + (a_2 + b_2)\xi^2 + (a_1 + b_1)\xi + a_0 = 0.$$

Noticing that

$$\begin{aligned} a_2 + b_2 &= d_1 + \beta y^* > 0, a_0 = d_1 d_3 \gamma z^* + \beta d_3 \gamma y^* z^* > 0, \\ (a_2 + b_2)(a_1 + b_1) - a_0 &= d_1 \beta^2 x^* y^* + \beta^3 x^* (y^*)^2 > 0, \end{aligned}$$

and by the Routh-Hurwitz criterion, we know that all roots of equation (5.4) have negative real parts. Thus we obtain the following result.

**Proposition 5.1.** *Suppose  $R_1 > 1$ . Then the HAM/TSP equilibrium  $P_2$  is locally asymptotically stable when  $\tau = 0$ .*

*Remark 5.2.* Using a Lyapunov function

$U(x, y, z) = (x - x^* \ln x) + (y - y^* \ln y) + \frac{\gamma}{\mu}(z - z^* \ln z)$ ,  
we can show that, if  $R_1 > 1$ , then the equilibrium  $P_2$  is globally asymptotically stable in the interior of  $\Gamma$  when  $\tau = 0$ .

Since when  $\tau = 0$ , all roots of the characteristic equation (5.3) lie to the left of the imaginary axis, a stability change at  $P_2$  can only happen when characteristic roots cross the imaginary axis to the right. We thus consider the possibility of purely imaginary roots  $\xi = i\omega$  ( $\omega > 0$ ) for  $\tau > 0$ . Substituting  $\xi = i\omega$  into equation (5.3) and separating the real and imaginary parts, we obtain

$$(5.5) \quad \begin{aligned} \omega^3 - a_1\omega &= b_1\omega \cos \omega\tau + b_2\omega^2 \sin \omega\tau, \\ a_2\omega^2 - a_0 &= b_1\omega \sin \omega\tau - b_2\omega^2 \cos \omega\tau. \end{aligned}$$

Squaring and adding both equations of (5.5) lead to

$$(5.6) \quad F(\omega) = \omega^6 + (a_2^2 - 2a_1 - b_2^2)\omega^4 + (a_1^2 - 2a_0a_2 - b_1^2)\omega^2 + a_0^2 = 0.$$

Let

$$(5.7) \quad G(u) = u^3 + (a_2^2 - 2a_1 - b_2^2)u^2 + (a_1^2 - 2a_0a_2 - b_1^2)u + a_0^2 = 0.$$

Therefore, if  $\xi = i\omega$  ( $\omega > 0$ ) is a purely imaginary root of equation (5.6), then the equation (5.7)

$$G(u) = 0$$

must have at least a positive root  $u = \omega^2$ . Notice that

$$G'(u) = 3u^2 + 2(a_2^2 - 2a_1 - b_2^2)u + (a_1^2 - 2a_0a_2 - b_1^2).$$

Let

$$\Delta = (a_2^2 - 2a_1 - b_2^2)^2 - 3(a_1^2 - 2a_0a_2 - b_1^2).$$

Note that  $G(0) = a_0^2 > 0$ . Then

(1) If  $\Delta \leq 0$ , noticing  $G(0) = a_0^2 > 0$ , and thus  $G(u)$  is monotonically increasing. Therefore, equation  $G(u) = 0$  has no positive roots, and all characteristic roots will remain to the left of the imaginary axis for all  $\tau > 0$ .

(2) If  $\Delta > 0$ , then the graph of  $G(u)$  has two critical points

$$(5.8) \quad u^* = \frac{-(a_2^2 - 2a_1 - b_2^2) + \sqrt{\Delta}}{3}, u^{**} = \frac{-(a_2^2 - 2a_1 - b_2^2) - \sqrt{\Delta}}{3}.$$

Obviously  $u^* > u^{**}$ , and if  $u^* < 0$ , then  $G(u) = 0$  has no positive roots.

(3) If  $\Delta > 0, u^* > 0$  and  $G(u^*) > 0$ , then  $G(u) = 0$  has no positive roots.

From (1), (2) and (3), We have the following theorem.

**Theorem 5.3.** *If (1\*)  $\Delta \leq 0$ , or (2\*)  $\Delta > 0, u^* < 0$ , or (3\*)  $\Delta > 0, u^* > 0, G(u^*) > 0$ . Then the HAM/TSP equilibrium  $P_2$  remains asymptotically stable for all  $\tau \geq 0$ .*

## 6 Numerical simulations

In this section, we shall carry out some numerical simulations for supporting our theoretical analysis. In the following, the data chosen are borrowed from Li and Shu [5].

Firstly, we consider the following set of parameter values:  $\lambda = 160$  cells/mm<sup>3</sup>/day,  $\beta = 0.002$  mm<sup>3</sup>/cells/day,  $d_1 = 0.2$  day<sup>-1</sup>,  $d_2 = 1.8$  day<sup>-1</sup>,  $d_3 = 0.5$  day<sup>-1</sup>,  $\mu = 0.2$  mm<sup>3</sup>/cells/day,  $\gamma = 0.2$  mm<sup>3</sup>/cells/day,  $\tau = 1$  day. For the above parameter set,  $R_0 = 0.8889 < 1$ , the system (1.2) has an unique infection-free equilibrium  $P_0 = (800, 0, 0)$ . Figure 1 shows  $P_0$  is globally asymptotically stable when  $R_0 < 1$ .

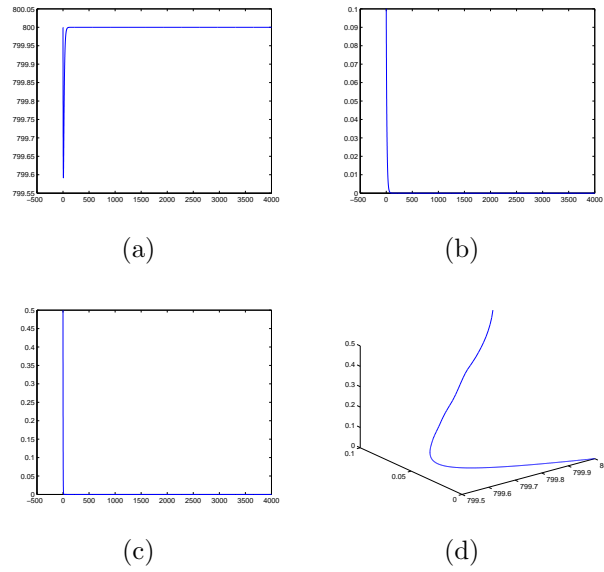


Figure 1:  $P_0$  is globally asymptotically stable. Here  $\lambda = 160$ ,  $\beta = 0.002$ ,  $d_1 = 0.2$ ,  $d_2 = 1.8$ ,  $d_3 = 0.5$ ,  $\mu = 0.2$ ,  $\gamma = 0.2$ ,  $\tau = 1$  and  $R_0 = 0.8889 < 1$ .

Next, we use the following parameters:  $\lambda = 165$  cells/mm<sup>3</sup>/day,  $\beta = 0.002$  mm<sup>3</sup>/cells/day,  $d_1 = 0.2$  day<sup>-1</sup>,  $d_2 = 1.64$  day<sup>-1</sup>,  $d_3 = 0.3$  day<sup>-1</sup>,  $\mu = 0.2$  mm<sup>3</sup>/cells/day,  $\gamma = 0.2$  mm<sup>3</sup>/cells/day,  $\tau = 3$  days. For those parameters,  $R_1 = 0.9912 < 1 < R_0 = 1.0061$ , the system (1.2) has a chronic-infection equilibrium  $P_1 = (820, 0.6098, 0)$ . Figure 2 demonstrates this chronic-infection equilibrium  $P_1$  is globally asymptotically stable when  $R_1 < 1 < R_0$ .

In figure 3, we adopt the following set of parameter values:  $\lambda = 160$  cells/mm<sup>3</sup>/day,  $\beta = 0.002$  mm<sup>3</sup>/cells/day,  $d_1 = 0.16$  day<sup>-1</sup>,  $d_2 = 1.9$  day<sup>-1</sup>,  $d_3 = 0.5$  day<sup>-1</sup>,  $\mu = 0.2$  mm<sup>3</sup>/cells/day,  $\gamma = 0.2$  mm<sup>3</sup>/cells/day,  $\tau = 3$  days. Thus  $R_1 = 1.0207 > 1$ , the system (1.2) has a chronic-infection equilibrium  $P_2 = (969.6970, 2.5, 0.1970)$  and  $\Delta = -0.0161 < 0$ . Figure 3 demonstrates  $P_2$  is asymptotically stable when  $R_1 > 1$  and  $\Delta < 0$ .

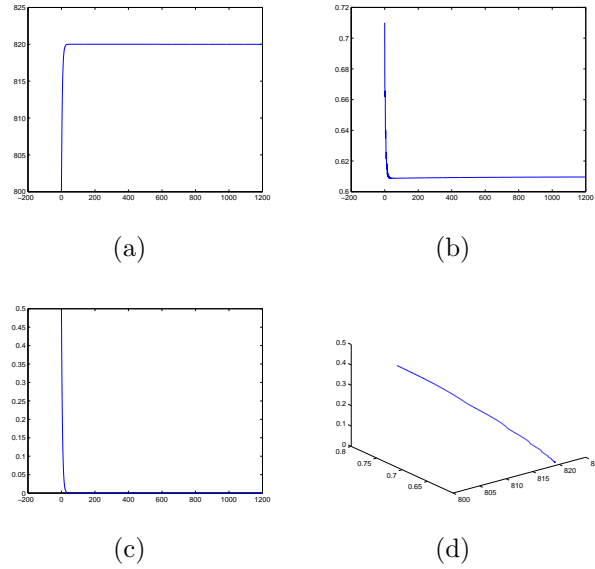


Figure 2:  $P_1$  is globally asymptotically stable. Here  $\lambda = 165, \beta = 0.002, d_1 = 0.2 \text{ day}^{-1}, d_2 = 1.64, d_3 = 0.3, \mu = 0.2, \gamma = 0.2, \tau = 3$  and  $R_1 = 0.9912 < 1 < R_0 = 1.0061$ .

In figure 4, we use the following parameters:  $\lambda = 160 \text{ cells/mm}^3/\text{day}$ ,  $\beta = 0.002 \text{ mm}^3/\text{cells}/\text{day}$ ,  $d_1 = 0.16 \text{ day}^{-1}$ ,  $d_2 = 1.85 \text{ day}^{-1}$ ,  $d_3 = 0.02 \text{ day}^{-1}$ ,  $\mu = 0.2 \text{ mm}^3/\text{cells}/\text{day}$ ,  $\gamma = 0.2 \text{ mm}^3/\text{cells}/\text{day}$ ,  $\tau = 3 \text{ days}$ . Thus  $R_1 = 1.0797 > 1$ , the system (1.2) has a chronic-infection equilibrium  $P_2 = (998.7516, 0.1, 0.7375)$  and  $\Delta = 0.0001 > 0, u^* = -0.0042 < 0$ . Figure 4 demonstrates  $P_2$  is asymptotically stable when  $R_1 > 1$  and  $\Delta > 0, u^* < 0$ .

In figure 5, the following parameter values are employed:  $\lambda = 160 \text{ cells/mm}^3/\text{day}$ ,  $\beta = 0.002 \text{ mm}^3/\text{cells}/\text{day}$ ,  $d_1 = 0.16 \text{ day}^{-1}$ ,  $d_2 = 1.7 \text{ day}^{-1}$ ,  $d_3 = 0.5 \text{ day}^{-1}$ ,  $\mu = 0.2 \text{ mm}^3/\text{cells}/\text{day}$ ,  $\gamma = 0.2 \text{ mm}^3/\text{cells}/\text{day}$ ,  $\tau = 3 \text{ days}$ . Thereby we obtain  $R_1 = 1.1408 > 1$  and the system (1.2) has a chronic-infection equilibrium  $P_2 = (969.6970, 2.5000, 1.1970)$ . Furthermore,  $\Delta = 0.0032 > 0, u^* = 0.0897 > 0, G(u^*) = 0.007 > 0$ . Figure 4 shows  $P_2$  is asymptotically stable when  $R_1 > 1$  and  $\Delta > 0, u^* > 0, G(u^*) > 0$ .

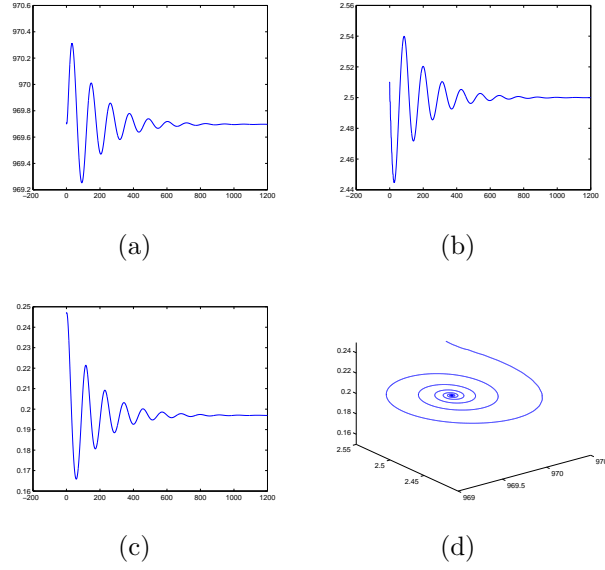


Figure 3:  $P_2$  is asymptotically stable. Here  $\lambda = 165, \beta = 0.002, d_1 = 0.16, d_2 = 1.9, d_3 = 0.5, \mu = 0.2, \gamma = 0.2, \tau = 3$  and  $R_1 = 1.0207 > 1, \Delta = -0.0161 < 0$ .

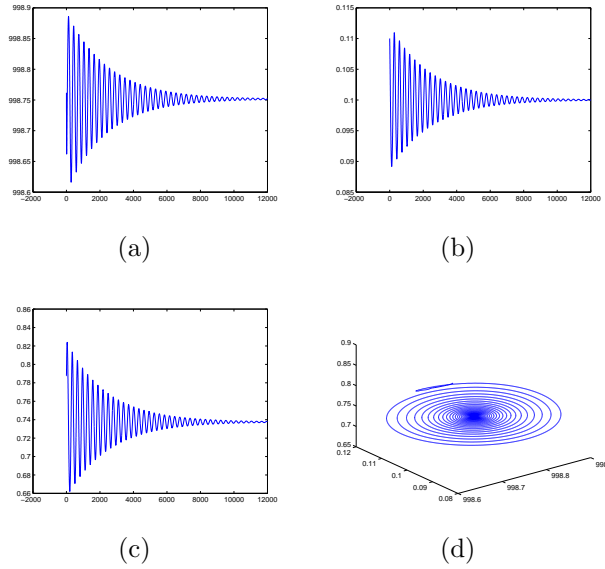


Figure 4:  $P_2$  is asymptotically stable. Here  $\lambda = 160, \beta = 0.002, d_1 = 0.16, d_2 = 1.85, d_3 = 0.02, \mu = 0.2, \gamma = 0.2, \tau = 3$  and  $R_1 = 1.0797 > 1, \Delta = 0.0001 > 0, u^* = -0.0042 < 0$ .

## 7 Conclusion

Based on the system (1.1), we propose the system (1.2) with delay, and investigate its dynamics. We roughly prove that  $P_0$  is globally asymptotically stable when  $R_0 < 1$

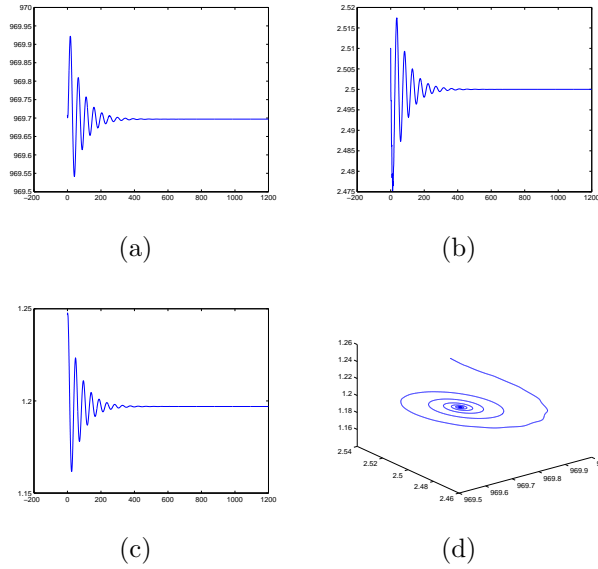


Figure 5:  $P_2$  is asymptotically stable. Here  $\lambda = 160, \beta = 0.002, d_1 = 0.16, d_2 = 1.7, d_3 = 0.5, \mu = 0.2, \gamma = 0.2, \tau = 3$  and  $R_1 = 1.0797 > 1, \Delta = 0.0032 > 0, u^* = 0.0897 > 0, G(u^*) = 0.007 > 0$ .

and  $P_1$  is globally asymptotically stable when  $R_1 < 1 < R_0$  by Lyapunov functionals. When  $R_1 > 1$ , we obtain  $P_2$  is asymptotically stable under certain conditions. At last, we carry out some numerical simulations to support the analysis results.

## Acknowledgments

The authors are grateful to the anonymous referee for his/her helpful comments and valuable suggestions, which led to the improvement of our manuscript.

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(Received February 1, 2013)